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SUMMARY WITH CRITICAL APPRAISAL

Silver Diamine Fluoride for the Prevention and Arresting of Dental Caries or Hypersensitivity: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines

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Context and Policy Issues

Silver diamine fluoride (SDF) was approved in February 2017 in Canada for the prevention and arrest of dental caries but it has been used for many decades in other countries like Japan.[1,2] The US FDA has approved SDF for treatment of tooth hypersensitivity.[1] It is available as 38% silver diamine fluoride in Canada and is applied as a topical agent making it less invasive than traditional procedures for treating caries; therefore, it is more appealing to younger patients or those with particular needs.

SDF is believed to have antimicrobial properties while promoting remineralization.[1] The literature has considered it as the "silver-bullet" with relatively minimal adverse events, such as tooth discolouration and some gingival irritation.[2] As a new agent in the Canadian market, it is important to consider its efficacy, safety and cost-effectiveness compared with currently available options.

The purpose of this report is to review the clinical and cost-effectiveness of silver diamine fluoride for the prevention and arrest of dental caries or hypersensitivity, as well as the guidelines for its use.

Research Questions

1. What is the clinical effectiveness of silver diamine fluoride (SDF) for the prevention of caries, caries arrestment, or for the treatment of tooth hypersensitivity in patients of any age?
2. What is the cost-effectiveness of SDF for the prevention of caries, caries arrestment, or for the treatment of tooth hypersensitivity in patients of any age?
3. What are the evidence-based guidelines associated with the use SDF for the prevention of caries, caries arrestment, or for the treatment of tooth hypersensitivity in patients of any age?

Key Findings

Five systematic reviews have noted benefits of using silver diamine fluoride for the arrest and prevention in dental caries in children and elderly patients. However, many of the studies that were included in the systematic reviews were small trials and were compared to placebo. Most of the systematic reviews did not provide a summary statistic; therefore, the overall magnitude of benefit for silver diamine fluoride is unknown. Adverse effects of silver diamine fluoride are generally not reported but some studies have suggested some irritation and staining. No serious adverse events have been reported. No evidence was identified for tooth hypersensitivity.

Generalizability to the Canadian context may be difficult. The studies were mostly conducted in Asia, which may have different needs compared to the Canadian population, especially for many subgroup populations that may be more vulnerable in Canada, including remote or populations, and the Canadian Aboriginal population.

One German economic evaluation demonstrated silver diamine fluoride is more cost-effective than fluoride rinses and chlorhexidine for the prevention of root-caries in the elderly. There were certain model assumptions that may make it difficult to apply to the Canadian population.

One clinical guideline from the Northwest Territories was identified that suggests silver diamine fluoride may have benefits; however, the benefit-harm assessment (net benefit rating) was unknown, and the rigour of guideline development was unclear. No recommendation is available as silver diamine fluoride was not approved at the time of publishing. One clinical guideline from the US was identified and it identified silver diamine fluoride as a useful agent in populations that would benefit from a less invasive approach or those who have trouble accessing dental professionals.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and June 8, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult and pediatric populations requiring treatment Sub-populations of interest: • 0-4 years of age (primary dentition) • 5-16 (mixed dentition) • 17 and over (permanent dentition) • Remote/isolated populations • First Nations and Inuit, Indigenous populations, Aboriginal population, American Indian/Alaska Native
Intervention	SDF (administered alone or in combination with tooth restorations, such as glass ionomer, amalgam and composite fillings; stainless steel crowns; or polycarbonate crowns)
Comparator	Q1-2: Other topical fluorides administered professionally in a dental provider office, such as gels and rinses; silver nitrate, placebo Q3: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., preventing caries, arresting of caries, decrease in hypersensitivity of teeth [dentine sensitivity], benefits, etc.) and safety (e.g., harms associated with its use, etc.) Q2: Cost-effectiveness Q3: Guidelines (e.g., indications, contraindications, limitations, safety issues for use of SDF in caries prevention, arresting of caries, dentine hypersensitivity, criteria or case selection for use [e.g., weight of child, etc.], impact of using SDF on the utilization of general anesthesia/deep sedation associated with other dental services, which healthcare provider should administer [e.g., dental hygienist, dentist, nurse, school nurse], etc.)
Study Designs	Health technology assessments, systematic reviews/meta-analyses, randomized controlled trials, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were individual studies published in a selected systematic review (SR), or were published prior to 2012.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR tool,[3] randomized studies were critically appraised using the Downs and Black checklist,[4] economic studies were assessed using the Drummond checklist,[5] and guidelines were assessed with the AGREE II instrument.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 500 citations were identified in the literature search. Following screening of titles and abstracts, 445 citations were excluded and 55 potentially relevant reports from the electronic search were retrieved for full-text review. 16 potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 60 publications were excluded for various reasons, while 11 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Details of the individual study characteristics are provided in Appendix 2.

Study Design

Five relevant SRs were identified and all investigated the management of dental caries.[7-11] The reviews were published in 2017,[7] 2016, [8] 2015,[9] 2013,[10] and 2012.[11] Between the five SRs, the literature searched covered from 1947 to January 2016.[7-11] Three SRs included only randomized controlled trials,[7-9] one specified clinical trials but did not report which type of studies,[10] and one included cohort studies and randomized controlled trials.[11] Some studies within the SRs overlapped (see Appendix 2, Table 5).

Three relevant randomized controlled studies that evaluated silver diamine fluoride (SDF) were identified.[12-14] One study investigated the development of new root caries compared with placebo,[12] and another study determined the discomfort associated with the application of SDF.[13] The third study was a randomized controlled trial that investigated the preventive and arresting effects on dental caries of SDF.[14]

One 2017 economic evaluation conducted a cost-effectiveness analysis, using a Markov model with a 10 year time horizon, of SDF compared with fluoride rinses, chlorhexidine, and placebo from the German healthcare perspective.[15]

One treatment protocol from the US[1] and one guideline from NT[16] were identified for the use of SDF.

Country of Origin

The investigators were based in USA and Puerto Rico for one of the SRs,[7] from Hong Kong, China for three of the SRs,[8,10,11] and from Germany for one of the SRs.[9] Two randomized trials were conducted in Hong Kong, China[12,14] and the second randomized trial looking at discomfort was conducted in Brazil.[13] The economic study was conducted in Germany.[15] One of the identified guidelines was funded through Health Canada's Territorial Health System Sustainability Initiative and developed by the Northwest Consultants for the Northwest Territories (NT), Canada, Department of Health and Social Services and the second was published for the University of California, San Francisco in USA.[1,16]

Patient Population

Three of the SRs included studies that were conducted in children, mostly with primary dentition but may have included some patients permanent teeth.[7,8,10] One of the SRs included studies that enrolled patients age 20 to 101, but it is unclear the age of those who received SDF.[9] One SR included children and elderly patients.[11]

Two randomized trials compared the effectiveness of SDF with placebo in community-dwelling elders.[12,14] One of the trials evaluated discomfort was conducted in children aged three to ten who have at least one active initial caries lesion on their primary molars.[13] The economic evaluation modelled cost-effectiveness in German elderly with varying risk of dental caries.[15] Patients aged 65 to 74 years old were considered and two groups of patients were evaluated, those with a high number of teeth at risk of caries (24 teeth), or those with a low number of teeth at risk of caries (16 teeth).[15]

The guideline from NT is intended for children and youth of NT as their overall dental health is worse than the average Canadian.[16] The American guideline identifies the patients that would be best treated with SDF, those who would be less suited for traditional interventions.[1]

Interventions and Comparators

One of the SRs included all preventative dental treatments and/or at least one chemical agent applied by professional or self and two of the included studies evaluated the effects of SDF compared to placebo.[9] The other four SRs included studies that considered SDF as an intervention and compared with placebo,[7,8,10,11] glass ionomer,[8,10] stannous fluoride,[10] and varying concentrations of SDF.[7,11]

In one randomized trial, annual application of 38% SDF was compared to placebo.[12] For a second randomized trial, 30% SDF was compared with placebo and resin infiltrant.[13] The third randomized trial compared the application of 38% SDF annually along with oral hygiene instructions and compared it to oral hygiene instructions alone and to a third group which received 38% SDF, oral hygiene instructions and oral hygiene education semi-annually.[14] The economic analysis compared the cost-effectiveness between SDF varnish, fluoride rinses, chlorhexidine, and placebo.[15]

Outcomes

The outcomes that were considered by the SRs included the following: arresting and preventing dental caries in primary dentition and permanent first molars,[7] remineralization of early enamel caries or white spot lesions,[8] arresting childhood dental caries,[8] clinical or

radiographic visible changes of active or inactive root caries,[9] management of early childhood caries,[10] and arresting and restoration of caries.[11]

One randomized trial evaluated the development of new root caries over 30 months while the second randomized trial evaluated discomfort associated with SDF application using the Wong-Baker faces scale.[12,13] The third randomized controlled trial assessed the effects of SDF on new active caries and the arrestment of root caries lesions.[14]

The outcome studied in the cost-effectiveness analysis was the cost per root caries-free tooth years.[15]

The guideline for NT considers preventative dental therapy.[16] The American guideline focuses on dental caries arrestment and prevention.[1]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

All five of the SRs were designed a priori and the search strategy was included.[7-11] Three of the studies indicated that there was more than one investigator for study selection and data selection,[7-9] while this process was less clear in the other two SRs.[10,11] Multiple databases were searched for three of the SRs,[7-9] but the other two SRs searched in one database.[10,11] Grey literature was included in one SR as an inclusion criteria.[8] Three SRs did not include grey literature.[7,9,11] It was unclear if grey literature was included in one of the SRs.[10] A list of the included studies was included in all five of the SRs.[7,8,10,11,17] However, only two of them included the list of excluded studies,[8,9] and the other three did not.[7,10,11] Three SRs included characteristics of the patients included in the studies,[7,9,11] and two of the SR did not provide such details.[8,11] Three of the SRs critically appraised and documented the studies that were included.[7-9] Two SRs did not assess and/or document the quality of literature.[10,11] Four of the SRs narratively described the results of the included studies and did not pool the data together for analyses.[7,8,10,11] One SR pooled the two relevant studies together for a summary statistic for the effectiveness of SDF.[9] There is indication of high heterogeneity between the two studies which may call into question the validity of the summary statistic.[9] Publication bias was assessed by one SR[8] and it is unclear the other four SRs considered publication bias.[7,9-11] Authors declared no conflict of interest in two of the SRs[8,9] while no information on conflict of interest was available from the other three SRs.[7,10,11]

Primary Studies

One of the randomized control trial clearly described the objectives, outcomes, interventions and comparisons within the methods section.[12] It was a well conducted double-blinded study where the methods were outlined thoroughly in the article. The sample size was powered to detect statistical differences between the groups. The authors declared no conflict of interest. However, there were some limitations that may make it difficult to generalize the results to the Canadian context. The water supply in the country of the study is fluoridated and this may be a affect the generalization of these results to communities that do no fluoridate the water. Adverse events associated with SDF were captured but not well documented. Although the study described the population, it is unclear if the baseline characteristics were similar between the different groups. It is also

unclear why participants dropped out or were lost to follow-up, which may introduce bias into the results.

The methodology, including the objectives, outcomes, interventions and comparisons, for the discomfort associated with SDF was well documented in one study.[13] A sample size calculation was completed to ensure it was powered to detect a difference between the groups. To determine discomfort, the Wong-Baker faces scale was used, which is a validated scale for pediatric patients. Results were logical and clearly described. However, there were some limitations to this study as this was a single blind study (only the children were blinded to the intervention received). There is no indication that the pediatric dentist was blinded and this can introduce bias into the results. Also, more girls were enrolled in the control group and it is possible there could be gender differences associated with discomfort with the treatments.

In the third randomized trial, the objectives, outcomes, intervention and comparisons were clearly described.[14] The sample size was powered to detect a difference between the interventions; however, it is a small sample of elders in Hong Kong, which may limit external validity of these results. Although the trial was double-blinded, because one group received additional oral hygiene education, it would be difficult to ensure allocation concealment. The baseline characteristics of the groups were not well described. Similar drop-out rates were noted between the three groups. The statistical tests were appropriate and the results were presented clearly in tables. Authors did not declare whether or not they had any potential conflicts of interest. Adverse events associated with SDF were not reported in the study.

Economic Evaluation

The economic evaluation was as cost-effective analysis.[15] The study clearly described the objectives, outcomes, intervention and comparisons and the choice of economic evaluation was appropriate. The model was clear, logical, and appropriate; it included the efficacy of treatments, which were derived from a systematic review, and a network meta-analysis was used to infer relative efficacies between treatments, cost of interventions and alternatives. The results and the details of the sensitivity analyses were provided and were appropriate for this evaluation. However, one of the major limitation is the results in the study are difficult to generalize to the Canadian population because the assumptions and costs are based on the German healthcare system. Additionally, the choice of a 10-year time horizon may not be ideal because it may be relevant to have information beyond this time frame. The evaluation also considered 24 teeth and 16 teeth as a high and low number of teeth at risk of caries based on German epidemiological data, which may be an assumption that is invalid for the Canadian population. It is also unclear if the willingness-to-threshold would be appropriate for the Canadian perspective. The costs and effectiveness of the treatments were provided; however, it is unclear how the incremental cost-effectiveness ratio (ICER) is calculated because it did not seem to correspond to the numbers provided.

Guidelines

The guideline developed for NT performed a systematic review of the literature; however, the description of the methodological details was not thorough, making it difficult to assess the rigour of the systematic review used to inform the guidelines.[16] The process for recommendation development was also not provided. No recommendation was provided for SDF as it was not yet approved in Canada when this guideline was published.

One guideline protocol was available for the prevention and arrestment of dental caries and it was developed at the University of California, San Francisco for their clinic use.[1] Since SDF is a relatively new agent in the US market, this protocol was intended to determine the population that would be indicated for SDF. A literature search was conducted for a systematic review; however, there was no critical appraisal of the evidence. The presented recommendations do not indicate the grade of the evidence, a limitation as it does not indicate how robust these recommendations are.

Summary of Findings

What is the clinical effectiveness of SDF for the prevention of caries, caries arrestment, or for the treatment of teeth hypersensitivity in patients of any age?

Overall, the five SRs indicate that SDF would be effective for the prevention of caries and caries arrestment in children and elderly patients compared to placebo.[7-11] However, the data was not pooled because the included individual studies are considered to be of low quality, with the exception of one SR that performed a meta-analysis. No studies reported on tooth hypersensitivity. Tooth discolouration was reported with the use of SDF in two of the SRs.[7,11] Adverse events were often not reported.

In addition to the SRs, three primary studies were identified. One study looked at the arrest rate of root caries in community-dwelling elders and found annual application of SDF resulted in better arrest rate than placebo at 90% compared to 45% at month 30 ($P < 0.001$).[12] No adverse effects were found on the teeth or soft tissues. The second study evaluated discomfort associated with the application of SDF compared to placebo and resin infiltration treatment of approximal caries lesions in children.[13] Children who received SDF experienced less discomfort using the Wong-Baker faces scale compared with those who received resin infiltration for treatment (relative risk [RR] 0.29, 95% confidence interval [CI] 0.12 to 0.71, P=0.006). The third study looked at the prevention of new root caries and the arrest of existing root surface caries at month 24 in community-dwelling elderly patients who received 38% SDF annually with oral hygiene instructions, 38% SDF annually with both oral hygiene instructions and oral hygiene education semi-annually, or only oral hygiene instructions.[14] Those who received SDF, oral hygiene instructions and oral hygiene education experienced a mean number of 0.70 (standard error [SE] 0.10) new root caries while those who only received oral hygiene instructions experienced a mean number of 1.33 (SE 0.21) new root caries, which was statistically different ($P = 0.033$). The group who received SDF and oral hygiene instructions but not semi-annual education had a mean number of 1.00 (SE 0.16) new root caries. The statistical significance of this is difference from the other groups was not reported. For the arrest of existing root caries surfaces, the group that received SDF with oral hygiene instructions arrested a mean number of 0.28 (SE 0.06) root caries surfaces while the one that received oral hygiene education as well arrested a mean number of 0.33 (SE 0.10) root caries surfaces. Both of these were better than the group that only received oral hygiene instructions, which experienced a mean arrest of 0.04 (SE 0.02) root surfaces ($P = 0.006$). Adverse events were not reported in this study.

What is the cost-effectiveness of SDF for the prevention of caries, caries arrestment, or for the treatment of teeth hypersensitivity in patients of any age?

One cost-effective analysis was identified evaluating German elderly patients from the healthcare system perspective which compared the cost-effectiveness between SDF, fluoride rinses, chlorhexidine, and no treatment.[15] In patients with a low number of teeth at

risk for caries (16 teeth), SDF was considered most cost-effective compared with no treatment for the prevention of root caries with an ICER of 8.30 Euros per root caries-free tooth year. For patients with a high number of teeth (24 teeth) at risk for caries, SDF was considered most cost-effective with an ICER of 0.79 Euro per root caries-free tooth year. In both groups, chlorhexidine and fluoride rinses were considered more expensive and less effective.

What are the evidence-based guidelines associated with the use SDF for the prevention of caries, caries arrestment, or for the treatment of teeth hypersensitivity in patients of any age?

Recommendations from the guidelines are summarized below and details are presented in Appendix 4.

The NT guideline intended to promoting better oral health for those residing in NT.[16] The summary evidence table reported that SDF is likely beneficial (moderate level of certainty) as a preventive therapy for primary teeth and permanent teeth, and that there seemed to be a low risk of harms; however, the studies supporting these conclusions were not cited in the table. The benefit-harm assessment (net benefit rating) was unknown. The rationale for the "unknown" rating was not described, though it may be linked to the uncertainty regarding adverse events or harms data. No recommendation was provided for the use of SDF as the intervention was not yet approved when the guidelines were developed.

One guideline was written by the School of Dentistry at the University of California, San Francisco.[1] It recognized that SDF is a new agent on the American market and its goal was to identify its clinical indication based on available evidence. The guideline stated that SDF is indicated in patients who require a less-invasive option and is much cheaper compared with traditional surgical measures for treatment of non-symptomatic active caries. The guideline further found that SDF may be indicated for those with limited access to dental care as it does not require subsequent monitoring. The guideline indicated that 38% SDF applied twice yearly is effective and less-costly compared to other options for arresting and prevention caries. SDF appeared to be well-tolerated, with some possible gingival irritation but it can darken and discolour teeth.

Limitations

Although the methodology of the included SRs are generally well conducted, the studies, however, that were included in these SRs are of lower quality and many of the trials are conducted in areas where there is fluoridation in the water, which may or may not apply to the Canadian context. A summary statistic for the effects of SDF is not provided for most of the SRs, making it difficult to know the magnitude of benefits associated with the treatment. Most of the studies evaluated the effects on childhood caries, primary dentition, or community-dwelling elderly patients and there is an absence of evidence for subpopulations that may be of interest of the Canadian context. Four of the SRs recognize the limitations of the available evidence and indicate that further research is needed for the effectiveness of SDF. Some of the studies provided oral hygiene instructions, which may include brushing or flossing. This may also limit external validity as these directions may influence and affect the prevention of dental caries. No evidence was found for the use of SDF for tooth hypersensitivity.[8-11]

Most studies generally evaluated the application of 38% SDF, but some used other concentrations and it is unclear if 38% is the optimal formulation that should be used. Although SDF is reported to be well tolerated, adverse events are not consistently reported

and no long term studies are available; therefore, there are still some unknowns regarding adverse events associated with SDF use.

Since it only recently became available on the Canadian market, limited clinical practice guidelines are published to provide recommendations that inform clinical decisions.

Conclusions and Implications for Decision or Policy Making

A total of 11 relevant publications were identified, including five systematic reviews,[7-11] three studies,[12-14] one economic evaluation,[15] and two clinical practice guideline.[1,16]

The available evidence overall indicates that SDF is an effective agent that can arrest and prevent caries in the pediatric and elderly population compared to placebo. It is a less invasive option and may be especially useful in patients who may not be suited for treatment with the traditional surgical techniques. The adverse events are not well reported in the evidence but when available, tooth discolouration is the primary adverse event reported.

One economic evaluation was available for the cost-effectiveness of SDF and it indicated that it is more cost-effective than fluoride rinse and chlorhexidine for the prevention of caries in a German elderly population.

A Canadian guideline from NT suggests that SDF likely has benefits for its children and youth population. However, the methods used to identify and evaluate the evidence informing this guideline were not clearly defined; therefore, these findings should be interpreted with caution. This guideline does not provide recommendations on the use of SDF. An American guideline of low-to-moderate quality was identified and suggests SDF would be a reasonable option for those who are better suited for a less invasive approach for the treatment and prevention of dental caries or those who have limited access to dental care.

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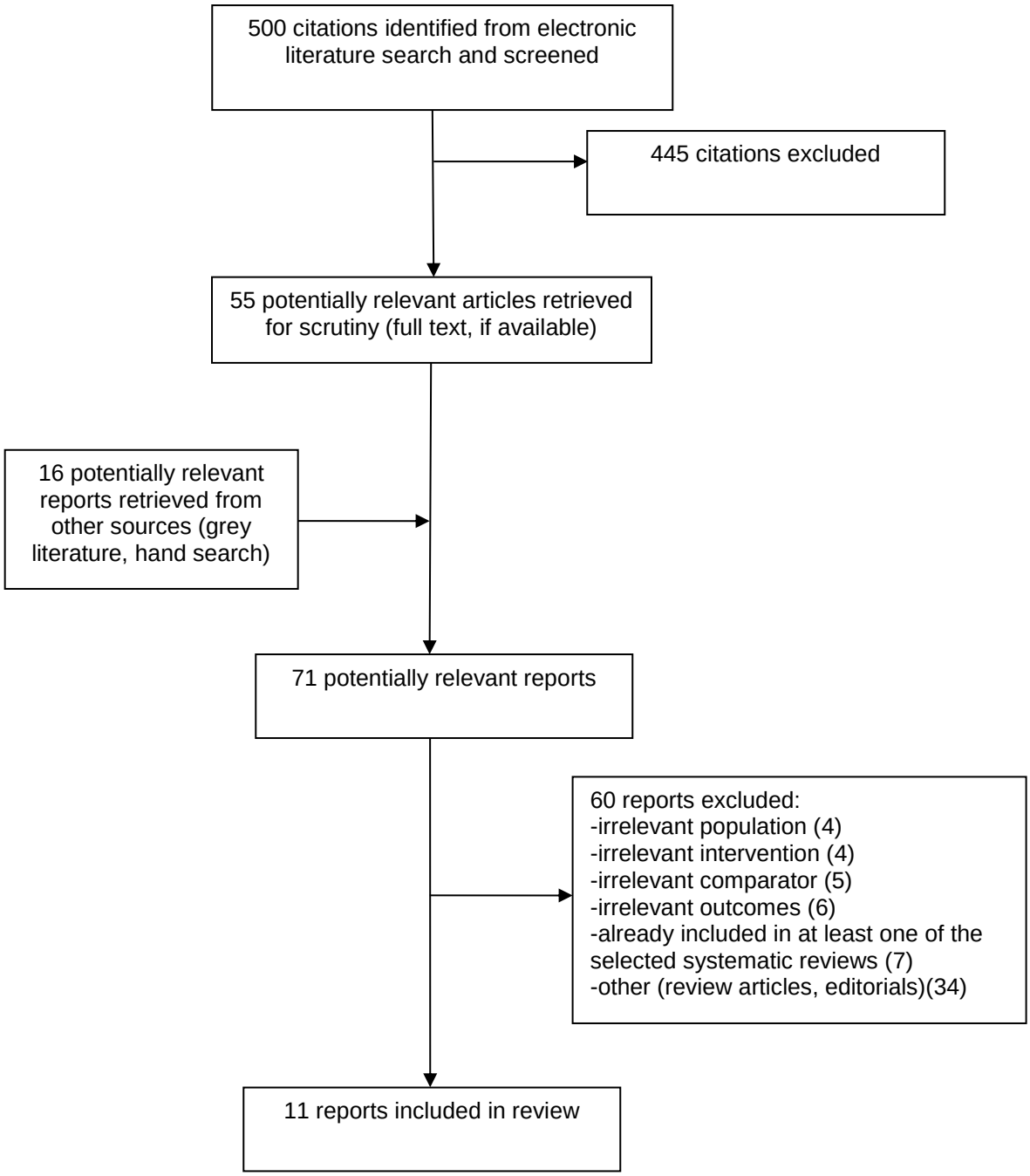
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 1: Characteristics of Systematic Reviews

First Author, Publication Year	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Contreras et al. 2017[7]	7 studies RCTs: • 1 study compared SDF vs. control (N=452) • 3 studies compared SDF vs. other treatments (N = 66, 91, 1016) • 1 study compared varying concentrations of SDF (N=976) • 2 studies compared SDF applied at different timings vs. other treatments (N=212, 304)	Conducted in school settings (kindergarten & primary school) Must be children with primary dentition and/or permanent first molars	SDF	Placebo, any other interventions, varying concentrations of SDF	Arresting and preventing dental caries in primary dentition and permanent first molars 12 to 36 months
Gao et al. 2016[8]	2 groups of RCTs: • Only 1 study (N=58) reviewed SDF in the group that looked at remineralization of early enamel caries. 9 other studies looked at other interventions & did not compare them with SDF • 5 studies (N=719, 6638, 1333, 1490, 1490) evaluated 38% SDF, 1 studied for 30% SDF and 1 other study (N=345) for silver fluoride were investigated for the outcome of arresting dentine caries.	Children, may be permanent or primary teeth	SDF	Placebo, glass ionomer	Two groups of studies: one group looked at the outcome of remineralization of early enamel caries or white spot lesions (follow up 1-30 months). Another group reviewed arresting childhood dental caries (follow up 12-30 months)

First Author, Publication Year	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Wierich et al. 2015[9]	Total of 30 included RCTs but only two of them included SDF as an intervention (N=264)	Age 20 to 101 years old (but for the entire study, unclear for SDF studies)	Preventative dental regimes and/or at least 1 chemical agents applied by professional or self-applied	Placebo, positive treatment or standard treatment	Clinical or radiographic visible changes of active or inactive root caries Median follow up: 15 months
Fung et al. 2013[10]	Total of 6 clinical trials for a total population of N=2095	Primary teeth only Age range: two to 13 years old	SDF	Placebo, stannous fluoride, glass ionomer	Manage early childhood caries Follow up ranges from 3 months to 24 months
Peng et al. 2012[11]	Total of 60 articles were identified for SDF: 36 *in vitro* studies, 14 clinical trials, 10 other types of articles including: • Two cohort studies • 6 RCTs	Primary and permanent teeth including children and elderly patients	SDF	Placebo, other agents, varying concentrations of SDF	Caries arresting and restoration Follow up ranges 6 months to 3 years

CADTH = Canadian Agency for Drugs and Technologies in Health; RCT = randomized controlled trial; SDF = SDF

Table 2: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Design, N	Population Characteristics	Intervention	Comparator(s)	Outcomes of Interest
Li et al. 2016[12] Hong Kong, China	RCT placebo parallel group design N = 83	Community-dwelling elders with at least one teeth with active root surface caries Mean age ± SD: 72.2 ± 5.8 years. 24.1% male.	Annual application of 38% SDF	placebo annual application of 38% SDF immediately followed by potassium iodide	Development of new root caries over 30 months
Mattos-Silveira et al. 2015[13] Brazil	RCT N = 141	Children aged 3 to 10 requiring dental treatment with at least one active initial caries lesion on approximal surface of the primary molars Mean age ± SD: 6.56 ± 1.69 years. 47.52% male.	SDF 30%	Placebo Resin infiltrant	Discomfort was reported using the Wong-Baker faces scale
Zhang et al. 2013[14] Hong Kong	RCT N=266	Community-dwelling elderly who were able to perform daily self-care activities, with at least 5 teeth exposed root surfaces Mean age ± SD: 72.5 ± 5.7 years. 25.6% male.	38% SDF annually for 2 years and oral hygiene instructions	Two groups: placebo with oral hygiene instructions; 38% SDF applied annually for 2 years and oral hygiene instructions and oral health education every 6 months	New active caries developed on exposed sound root surfaces & arrestment of root caries lesions found at baseline becomes an inactive lesion

CADTH = Canadian Agency for Drugs and Technologies in Health; RCT = randomized controlled trial; SDF = silver diamine fluoride

Table 3: Characteristics of Included Economic Studies

First Author, Publication, Year, Country	Type of Analysis, Perspective, Time Horizon	Study Population	Intervention, Comparator, Outcomes	Main Assumptions
Schwendick et al. 2017[15] Germany	Cost-effective analysis Mixed public-private payer perspective 10 years	Two groups: one with a high number of teeth at risk (24 teeth), one with a low number of teeth at risk based on epidemiological data for elderly German with varying risk for dental caries	SDF varnish compared with no treatment, 225-800 ppm fluoride rinses, chlorhexidine Cost per root caries-free tooth year	• Patients with 24 teeth at risk of dental caries is considered high number of teeth at risk while those with 16 teeth at risk is considered low number of teeth at risk. • Tooth-level risk of caries is equal between all teeth and groups. • Costs for rinses assume 15 ml being used daily. • Costs are based on German healthcare system where fluoride varnishes are very low.

CADTH = Canadian Agency for Drugs and Technologies in Health; RCT = randomized controlled trial; SDF = silver diamine fluoride

Table 4: Characteristics of Included Guidelines

Objectives			Methodology			
Target Population, Intended Users	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence Collection, Selection and Synthesis**	**Evidence Quality Assessment**	**Recommendations Development and Evaluation**	**Guideline Validation**
NT guidelines 2014[16]						
Children and youth in NT with primary and permanent teeth, Dental professionals in NT	SDF	Preventative oral therapy	Systematic review but few details are provided	Unclear	Unclear	Unclear
Horst et al. 2016[1]						
American dental professionals	SDF for caries arrestment	Caries arrestment, caries prevention	Literature search, consultation with experts in cariology and material chemistry	Unclear	Unclear	Unclear

CADTH = Canadian Agency for Drugs and Technologies in Health; RCT = randomized controlled trial; SDF = silver diamine fluoride

Table 5: Overlap in Included Studies between Systematic Reviews

Study author (year of publication)	Systematic Reviews				
	Contreras et al. (2017)[7]	Gao et al. (2016)[8]	Wierichs et al. (2015)[9]	Fung et al. (2013)[10]	Peng et al. (2012)[11]
Nishino (1969)					✓
McDonald (1994)				✓	✓
Gotjamanos (1996)				✓	
Lo (2001)		✓			
Chu (2002)		✓		✓	✓
Llodra (2005)	✓	✓		✓	✓
Braga (2009)	✓				✓
Yee (2009)	✓	✓		✓	✓
Tan (2010)			✓	✓	✓
Singha (2011)					✓
Dos Santos (2012)	✓	✓			
Monse (2012)	✓				
Zhi (2012)	✓	✓		✓	
Zhang (2013)			✓		
Duangthip (2016)	✓				

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[3]

AMSTAR Item		Contreras et al. 20177	Gao et al. 20168	Wierich et al. 20159	Fung et al. 201310	Peng et al. 201211
Was an a priori design provided?		+	+	+	+	+
Was there duplicate study selection and data extraction?	Selection	+	+	+	?	?
	Extraction	+	+	+	?	?
Was a comprehensive literature search performed?		+	+	+	X	X
Was the status of publication (i.e. grey literature) used as an inclusion criteria?		X	+	X	?	X
Was a list of studies (included and excluded) provided?	Included	+	+	+	+	+
	Excluded	X	+	+	X	X
Were the characteristics of the included studies provided?		+	X	+	+	X
Was the scientific quality of the included studies assessed and documented?		+	+	+	X	X
Was the scientific quality of included studies used appropriately in formulating conclusion?		+	+	+	?	+
Were the methods used to combine the findings of studies appropriate?		?	?	+	?	?
Was the likelihood of publication bias assessed?		?	+	?	?	X
Was conflict of interest included?		X	+	+	X	X

Table 7: Strengths and Limitations of Randomized Controlled Trials Downs and Black[4]

Strengths	Limitations
Li et al. 2016[12]	
• The objectives, outcome of interest, interventions and comparators were clearly described in the methods section. • Inclusion and exclusion criteria were defined and appropriate for the population of interest. • Power calculation was done to determine sample size and potential drop out was accounted for. • Data analysis was appropriate for the objective of the study. • Results were described clearly and conclusion was logical. • Study was double blinded and appropriate measures (ie. Adding bitter flavour to placebo to minmic the taste of SDF) were in place to maintain blinding throughout the study. • The investigators declared no conflict of interest.	• It is unclear if the groups were similar at baseline as this is not provided in the study. • Adverse events were captured but very little information is available in the study. • Water supply is fluoridated in the country of the study; therefore, it is unclear if these results can be generalized to areas where the water is not fluoridated. • The drop-out rate was described in the study; however, it is less clear why the participants had dropped out.
Mattos-Silveira et al. 2015[13]	
• Clearly stated the objectives and the outcomes of interest for the study. • The intervention and comparisons are clearly described. • Children were randomly allocated to the treatment groups. • Authors have no conflict of interest. • Patients were recruited from the population of interest for the study. • Wong-Baker faces scale was used and is a validated took for pediatrics. • Sample size calculations were done and the study was powered to find a difference. • Appropriate statistical tests were conducted to determine if there were differences in the children's comfort between the different treatments. • Results were clearly described and included estimates of random variability.	• Most patient characteristics are described. • Only the children were blinded, there is no discussion if the trained pediatric dentist applying the therapy is blinded. • Potential for bias as the resin infiltration treatment takes longer than the others and this may result in loss of blinding for the children in the study. • At baseline, there were more girls in the control group and gender may be a confounding factor.
Zhang et al. 2013[14]	
• Clearly stated the objectives and the outcomes of interest in the methods for the study. • The intervention and comparisons are clearly described. • Power calculation was done to determine appropriate sample size. • Appropriately recruited participants from the population of interest. • Trial was double-blinded and the investigators tried to take appropriate measures to maintain blinding. • Statistics that were used appears to be appropriate. • Similar rates of drop-out between the groups. • Results are presented clearly in text and in the tables.	• It is unclear if the baseline characteristics were similar between groups as it was not documented. • It is difficult to maintain blinding since one group received extra oral hygiene education. • Safety information was not measured nor documented in the study. • Authors did not declare their conflicts of interest. • Study is conducted in Hong Kong, it is difficult to generalize to the Canadian population. • Sample size is small and may limit external validity.

Table 8: Strengths and Limitations of Guidelines using AGREE II[6]

Item	Guideline	
	Horst et al. 2016[1]	NT 2014[16]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	+	+
2. The health question(s) covered by the guideline is (are) specifically described.	+	+
3. The population (patients, public, etc.) to whom the guideline is meant to apply to specifically described.	-	+
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	+	+
5. The views and preferences of the target population (patients, public, etc.) have been sought.	?	?
6. The target users of the guideline are clearly defined.	-	+
Domain 3: Rigour of Development		
7. Systematic methods were used to search the evidence.	+	?
8. The criteria for selecting the evidence are clearly described.	+	-
9. The strengths and limitations of the body of evidence are clearly described.	-	-
10. The methods for formulating the recommendations are clearly described.	-	-
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	+	+
12. There is an explicit link between the recommendations and the supporting evidence.	?	-
13. The guideline has been externally reviewed by experts prior to its publication.	?	?
14. A procedure for updating the guideline is provided.	-	-
Domain 4: Clarity of Presentation.		
15. The guideline describes which options are appropriate in which situations and in which population groups, as informed by the body of evidence.	+	+
16. The guideline describes the different options for managing the condition or health issue.	-	-
17. The guideline presents the key recommendations so that they are easy to find.	+	-
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	+	-
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	+	+
20. The potential resource implications of applying the recommendations have been considered.	-	+

21. The guideline presents monitoring and/or auditing criteria.	-	-
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	?	?
23. Competing interests of guideline development group members have been recorded and addressed.	+	-

Legend: + = Yes, X = No, ? = Unclear

Table 9: Strengths and Limitations of Economic Studies using Drummond[5]

Strengths	Limitations
Schewendicke et al. 2017[15]	
• Clearly stated the question of interest, intervention and appropriate comparators, outcomes of interest and the perspective. • Choice of economic evaluation was appropriate for the question addressed. • Efficacy of the treatments were estimated based on recent systematic review and when values were not available for direct comparisons, network meta-analysis was used to determine relative efficacies. • Costs of interventions and alternatives clearly identified. • Currency, price date and details for discounting were provided. • Model was clearly described and logical. • Details were provided for the sensitivity analyses and the approach is appropriate.	• Difficult to generalize the results to Canada as the assumptions and costs are based on the German healthcare system. • 10-year time horizon was used, may not be long enough unless looking at an older population. • It is unclear how ICER is calculated in the study as the numbers for costs and effectiveness do not correspond to the calculated ICERs presented in the results. • The scenario of high number (24 teeth) vs. low number (16 teeth) of teeth at risk for dental caries is an assumption that is reasonable for the German elderly population as indicated by their epidemiological data. It is unclear whether or not this assumption is applicable to the Canadian context. • Unclear if the willingness-to-pay threshold that is used in German healthcare system would be appropriate for the Canadian healthcare system. • Costs were all from German settings, from 2016, and dental costs can be highly variable. These results may be different if costs were obtained from a different source given fluoride varnishes are relatively inexpensive in Germany.

ICER = incremental cost-effectiveness ratio

Appendix 4: Main Study Findings and Author's Conclusions

Table 10: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusion
Contreras et al. 2017[7]	
• No pooling of data was performed. • One study reported 38% SDF was more effective than placebo for caries reduction (80% vs. 65%). One study demonstrated 10% SDF was significantly better than cross-toothbrushing technique and glass ionomer cement for arresting caries. One study demonstrated higher concentration (38%) of SDF is better at arresting surface caries compared to lower concentration (12%) and placebo at month 6, 12 and 24. One study demonstrated 30% SDF is 1.73 times (95% CI 1.38 to 2.18, P<0.05) more effective at stopping caries than interim restorative technique. One study showed semi-annual application of SDF demonstrated higher caries arrest rate compared with annual and glass ionomer cement application (OR 2.98, 95% CI 1.35 to 6.69, P=0.007). One study demonstrated at month six and twelve, semi-annual application of SDF resulted in arrest rates for caries compared to annual application; however, at month 18, the annual application group resulted with higher rates of arrest (40%, P < 0.001) compared to more intensive application. One study looked at 38% SDF compared to atraumatic restorative treatment in toothbrushing and nontoothbrushing children. Caries increment was reported to be lower in the group that received atraumatic restorative treatment compared to SDF in both nontoothbrushing (HR 0.33, 95% CI 0.20 to 0.54, P <).001) and toothbrushing children (HR 0.12, 95% CI 0.02 to 0.61, P < 0.01). • Adverse events were not reported in most studies. Black discolouration was reported in two studies.	*"A systematic review of 7 studies indicated that SDF, at concentrations of 30% and 38%, is more effective than other preventive management strategies for arresting dentinal caries in the primary dentition."* (p28)[7] "*Additionally, 30% and 38% concentrations of SDF show potential as a caries preventive treatment in primary teeth and permanent first molars*." (p28)[7]
Gao et al. 2016[8]	
• Results were divided into two groups based on the outcome that was study: remineralization of early enamel caries and arresting dentine caries. • No pooling of data was performed for evaluating SDF for remineralization of early enamel caries because there was only one relevant study was found and it concluded 10% SDF, glass ionomer restoration and tooth-brushing were all similar for remineralization of early enamel caries. • Seven studies were included that evaluated arresting dentine caries and it indicated that 38%, 30% and 12% of SDF were better than placebo. Two studies found 38% SDF to be more effective than sodium fluoride for arresting of dentine caries. Two studies demonstrated SDF is more effective than glass ionomer restorations. Five studies that used 38% SDF were combined in a meta-analysis and it can reduce caries by 65.9% (95% CI 41.2% to 90.7%, P < 0.001) when compared with no treatment or glass ionomer. Of note, the application of SDF varied between these studies. But all studies	"*SDF solution at 38 % is effective in arresting active dentine caries. Because the number of clinical trials that studied the arresting effect of dental caries is limited, more clinical trials should be performed*." (p8)[8]

Main Study Findings	Author's Conclusion
accounted for equal weight for the summary statistic. • Indicates there appears to be no serious adverse events but more studies are needed.	
Wierich et al. 2015[9]	
• Two studies were pooled (N=264) to show SDF is more effective than placebo for reducing decayed, missing, filled root surfaces or new root caries lesions (mean difference -0.33, 95% CI -0.39 to -0.27, P<0.00001) in adults, likely reducing the initiation of new root caries lesions. • The quality of the studies for SDF in general were considered to be very low. • No information about adverse events for SDF is provided.	*"Based on meta-analysis, dentifrice containing 5,000 ppm F- and professionally applied CHX or SDF varnish may inactivate existing and/or reduce the initiation of RCLs. However, results should be interpreted with caution, due to the low numbers of clinical trials for each agent, the high risk of bias within studies, and the limiting grade of evidence.*" (p269)[9]
Fung et al. 2013[10]	
• Although a list of the included studies were provided, little information is provided regarding the study design. • No pooling of data was performing. • Four of the six studies demonstrated SDF, ranging in frequency of application and concentration, to arrest dentine carries in primary teeth compared with control. • Little information regarding adverse events were presented.	"*Clinical studies have demonstrated that 38% SDF is effective in arresting ECC. There was no significant complication reported in association with SDF treatment."* (p4)[10] "*Because SDF therapy is painless, simple, and low-cost, it could be widely recommended and promoted as an alternative preventive treatment to conventional invasive caries management, especially among child patients who are too young for conventional dental care or those with special needs, or those with difficulty accessing and affording conventional dental care*." (p4)[10] "*More well-designed clinical trials on SDF for arresting dental caries are necessary to provide sound and convincing evidence*." (p. 4)[10]
Peng et al. 2012[11]	
• No pooling of data was performing. • In the six randomized controlled trials, four of the studies demonstrated SDF was more effective at arresting caries and preventing dentine caries in primary teeth. One study showed that oral hygiene instruction was not as effective as chlorhexidine, sodium fluoride or SDF for caries prevention. The last study suggested glass ionomer fissure sealant and SDF could be as effective as calcium hydroxide as indirect pulp capping materials. • For adverse events, staining and possible pulp irritation can occur but can be minimized by diluting the SDF solution, but it is unclear what the dilution should be.	"*In clinical trials, SDF has been shown to have caries arresting properties, with most of the studies performed on primary teeth and some later ones on permanent molars.*" (p536)[11] "*A range of concentrations of silver compounds have been used in dentistry including…38 wt% SDF and 12 wt% SDF. However, there is no clinical basis for choosing these concentrations. Studies which investigate the clinical efficacy of concentration gradients and the minimal effective concentration are therefore appropriate for further study."* (p536)[11]

SDF = silver diamine fluoride; CI = confidence interval

Table 11: Summary of Findings of Included Clinical Effectiveness Studies

Main Study Findings	Author's Conclusion
Li et al. 2016[12]	
• At month 30, arrest rate of root caries was 45%, 90% and 93% in the placebo, SDF and SDF/potassium iodide groups respectively. Both SDF and the SDF/potassium iodide group significantly arrested root caries when compared with placebo (P<0.001). No difference was observed between the SDF group and the SDF group/potassium iodide groups (P>0.05). • In terms of harm, no adverse effects were found on teeth or soft tissues.	"*…it is concluded that applications of SDF solution or SDF/KI solution are effective in arresting active root caries. Application of KI does not affect the effectiveness of SDF in arresting root caries and also does not reduce the black staining*." (p19)[12]
Mattos-Silveira et al. 2015[13]	
• Compared to the children who received the resin infiltration, those who received SDF experienced less discomfort (RR 0.29, 95% CI 0.12 to 0.71, P=0.006).	"*Even among minimal invasive approaches, the children's acceptability may vary due to child's felt discomfort*." (p304)[13] "*Techniques that promote less discomfort, as application of SDF, should be preferred and considered in further clinician's decision-making*." (p304)[13]
Zhang et al. 2013[14]	
• After 24 months, the mean number of new root caries surfaces were 1.33 (SE 0.21) in placebo, 1.00 (SE 0.16) in the group receiving 38% SDF with oral hygiene instructions and 0.70 (SE 0.10) in in the group receiving 38% SDF with oral hygiene instructions and oral health education. It was statistically lower in the third group compared to place (P < 0.033). • For the arrestment of root caries surfaces, both groups with SDF were better than the placebo group with only oral hygiene instructions. SDF with oral hygiene instructions arrested a mean of 0.28 (SE 0.06) root caries surfaces while the group that also had oral hygiene education arrested a mean of 0.33 (SE 0.10) root caries surfaces and in placebo, a mean of 0.04 (SE 0.02) root surfaces were arrested (P = 0.006).	"*In summary, this 24-month clinical study reports for the first time that synergetic applications of SDF solution and OHE annually were more effective than giving OHI alone in preventing and arresting root caries among community-dwelling elderly subjects."* (p290)[14]

SDF = silver diamine fluoride; SE = standard error

Table 12: Summary of Findings of Included Economic Studies

Main Study Findings	Author's Conclusion
Schwendicke et al. 2017[15]	
• When considering those with 16 teeth at risk of dental carries, no preventive treatment is considered to be the least costly but also least effective (130 Euros, 144 years) while SDF is ranked next (180 Euros, 151 years), with an ICER 8.30 Euros per root caries-free tooth year. SDF is considered most cost effective because chlorhexidine and fluoride rinses are both more costly and less effective compared to SDF. • In a population with 24 teeth at risk of dental caries, similar ranking is found. For no treatment, it is the least costly and also least effective (197 Euros, 217 years) and for SDF it is considered most cost-effective (204 Euros, 226 years) with an ICER of 0.79 Euro per root caries-free tooth year. Similarly, both chlorhexidine and fluoride varnishes cost more and were less effective.	"*The present study found SDF varnish the most effective, but not always the least costly option. Only in individuals with a high number of teeth at risk or high risk per tooth, SDF was both more effective and less costly than not providing any preventive treatment. Neither CHX varnish nor daily fluoride rinsing were cost-effective in our study*." (p62)[15]

SDF = silver diamine fluoride; ICER = incremental cost-effectiveness ratio; CHX = chlorhexidine

Table 13: Summary of Findings of Recommendations Included Guideline

Findings and Recommendations	Quality of Evidence, Strength of Recommendation
Horst et al. 2016[1]	
"Silver diamine fluoride is a safe, effective treatment for dental caries across the age spectrum. At UCSF it is indicated for patients with extreme caries risk, those who cannot tolerate conventional care, patients who must be stabilized so they can be restored over time, patients who are medically compromised or too frail to be treated conventionally, and those in disparity populations with little access to care."(p. 11)[1]	There was no critical appraisal of the evidence and there was not direct correlation between the literature and the recommendations. No grading was provided for the recommendations.
NT Guidelines, 2014[16]	
Benefit-harm assessment (net benefit rating) of SDF as a preventative therapy in primary teeth and permanent teeth: *"unknown; benefits likely" (Table 10, part 4)* *"Unable to make recommendation, not yet approved." (Table 10, part 4)*	Evidence was not clearly linked to the benefit-harm assessment. No recommendation provided.

SDF = silver diamine fluoride; UCSF = University of California, San Francisco;